REMARKS

I. Status of the Claims

In response to the restriction requirement, Applicants elected Group I, claims 1, 2 and 4, drawn to a method of identifying a compound that modulates the binding of CEL (carboxylester lipase) to a receptor. Thus, Claims 1, 2 and 4 are under consideration, and claims 3, 5, 6, 8 and 9 stand withdrawn.

The claims are objected to and stand rejected under 35 U.S.C. §112, first and second paragraphs and 35 U.S.C. §102. The specific grounds for rejection, and applicants' response thereto, are set out in detail below.

Claim 2 is canceled herein, claims 1 and 4 are amended, and new claims 10-21 are added. Support for the amendments and new claims are as follows:

Claim 1 - "decrease" (page 6, lines 1-3); receptor types (page 7, lines 3-14)
Claim 4 - "reduction of retention of lipoproteins" (original claim 4, page 6, lines 13-19)
Claims 10-13 - receptor types (page 7, lines 3-14)
Claims 14-21 - nature of the assays (page 6, lines 26-37)

II. Objections

A. Sequence Listing

Applicants are submitting a new sequence listing to address the perceived deficiencies in the original sequence listing. Reconsideration and withdrawal of the objection is therefore respectfully requested.

B. Specification

Applicants have amended both the title of the application and the descriptions for FIGS. 4 and 5. Reconsideration and withdrawal of the objection is therefore respectfully requested.

C. Oath Declaration

Applicants are providing a newly executed Oath & Declaration herewith. Reconsideration and withdrawal of the objection is therefore respectfully requested.

D. Claims

Applicants believe that the claims, as presented for reconsideration, overcome each of the claim objections. Reconsideration and withdrawal of the objection is therefore respectfully requested.

III. Overview of the Invention

A. Atherogenesis

Atherogenesis is the process of formation of atherosclerotic plaques on the endothelium of the vascular system (*i.e.*, on the surface of the walls of blood vessels). It is well established that atherosclerotic plaques form as a consequence of the accumulation, by cells of the vascular endothelium, of modified forms of lipoproteins (atherogenic lipoproteins) which are recruited from the plasma within the vascular system. This is discussed in the present application on page 1, lines 13 to 16.

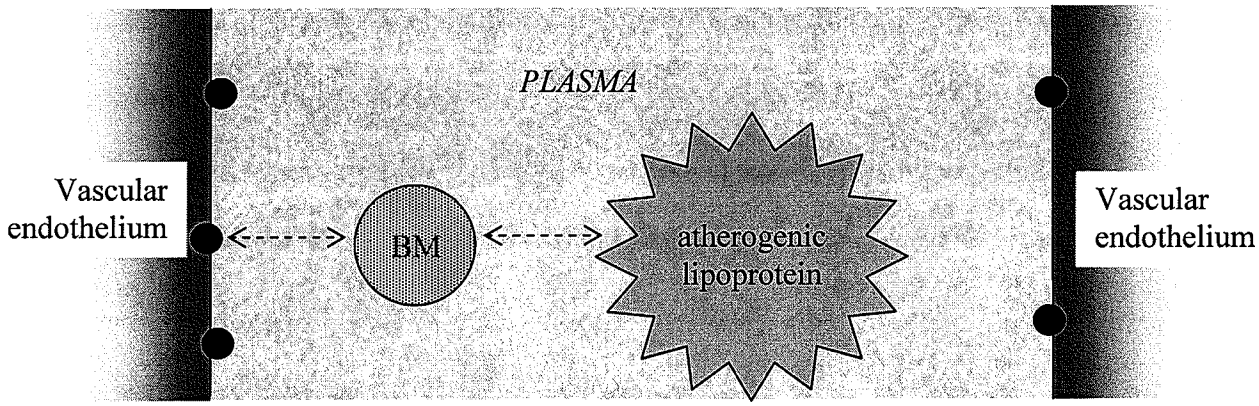
Also, Pentikäinen *et al*, 2002, *Atherioscler. Thromb. Vasc. Biol.*, **22**, 211-217 (cited in the IDS on file), as cited at page 2, lines 26-36 of the present application, reports in the abstract that:

> For low density lipoprotein (LDL) particles to be atherogenic, increasing evidence indicates that their residence time in the arterial intima must be sufficient to allow their modification into forms capable of triggering extracellular and intracellular lipid accumulation.

Thus, atherogenesis follows from the accumulation and retention of atherogenic lipoproteins within the vascular endothelium (*i.e.*, within the "arterial intima"). Also, page 2, lines 1-3 of the present application, explains that "... [S]ubendothelial retention of atherogenic lipoproteins is the

trigger for all of these processes." Thus, the process of atherogenesis ***requires interaction*** between cellular components of the vascular endothelium and atherogenic lipoprotein components from the plasma. The art (as discussed in more detail below) has previously identified "***bridging molecules***" that are able to promote this interaction, by binding to components both in the endothelium and in the plasma, and thus promote the onset or development of atherogenesis.

In very general terms, the role of "bridging molecules" in the promotion of atherogenesis can be envisaged as shown in the following schematic (showing a longitudinal cross-section of a blood vessel lumen, with vessel walls at either side) –



BM = bridging molecule
● = endothelial surface molecule/receptor
<-> = binding affinity

B. Art-known Mechanisms of Retention of Atherogenic Lipoproteins

As discussed at page 17, lines 1-8 of the present application:

> One important process that has been implicated in the early stages of atherosclerosis is subendothelial retention of atherogenic lipoproteins (reviewed in William and Tabas, 1995). ApoB is the apolipoprotein associated with the atherogenic lipoprotein LDL, and it has been suggested that the atherogenicity of apoB-containing LDL may be linked to the affinity of apoB for artery wall proteoglycans, leading to retention of the LDL particle in the subendothelial space

> (Skalen *et al.*, 2002). ***The binding of apoB-containing lipoproteins to extracellular proteoglycans is facilitated by lipoprotein lipase (LPL) which acts as a molecular bridge*** between the subendothelial proteoglycans and lipoproteins (Pentikainen *et al.*, 2002).

Emphasis added. Thus, at least one "molecular bridge", namely LPL, had already been suggested by the art to be involved in facilitating the sub-endothelial retention of atherogenic lipoproteins. Also, attention is directed to Gustafsson *et al*, January 2004, *Cell. Mol. Life Sci.*, 61, 4-9 (cited in the IDS on file) which generally reviews the role of retention of atherogenic lipoproteins in the development of atherogenesis (as is self-evident from its title). In particular, page 6, 2nd column, 2nd paragraph reports that:

> Lipoprotein lipase (LPL) which is secreted by smooth muscle cells and macrophages in atherosclerotic lesions [31], has been ***shown to act as a bridge*** between GAG and extensively oxidised LDL...The bridging function of LPL ***does not require catalytic activity.***

Emphasis added. Figure 2 of Pentikäinen *et al* also illustrates how LPL is thought to act as a bridging molecule.

C. The Present Invention

The present inventors are the first to realise that ***CEL can act as a "bridging molecule"*** to promote the interaction between the endothelium and plasma-derived atherogenic lipoprotein components. Please see the present application at page 17, lines 10-14, which reports that:

> The notion that affinity to vascular proteoglycans is a determinant of subendothelial retention invokes another potential role for the CEL associated with LDL. The N-terminal part of the CEL protein contains a region which binds avidly to heparin and several heparin variants (Falt et al. 2001), and while the binding of CEL to vascular proteoglycans remains to be investigated, ***CEL emerges a possible candidate for another bridging molecule.***"

Emphasis added. This realisation was based on a new appreciation of the ability of CEL to bind to ***both*** of endothelial and plasma-derived atherogenic lipoprotein factors.

- Figures 5B and 5C (as also discussed at page 12, lines 28-31) of the present application demonstrates that CEL associates with HDL/LDL-fractions in the plasma. Thus, the inventors have shown that CEL can bind to atherogenic lipoproteins (that is, high and low density lipoproteins) present in the plasma. This is also discussed at page 16, lines 5-10 of the present application.

- Additionally, as discussed at page 16, lines 1-2 of the present application, CEL can associate with apoB, which is the protein component of lipoproteins within the plasma.

- Furthermore, as discussed at page 17, lines 11-12 of the present application, the N-terminal part of CEL binds avidly to heparin and several of its variants, which are key structures in proteoglycans found on the surface of vascular endothelium.

- Likewise, as discussed in the present application at page 17, lines 14 *et seq*, CEL can bind to the scavenger receptor LOX-1 which is clearly a component of vascular endothelial cells (as supported by Moriwaki *et al*, 1998, *Arterioscler. Thromb. Vasc. Biol.*, 18, 1541-1547, as cited in the IDS on file; see abstract, 2nd sentence which reports that LOX-1 was identified "in vascular endothelial cells").

Similarly, CEL present in lipoprotein particles has the potential to act as a bridging molecule by binding to other receptors, as claimed.

- Camarota *et al*, June 2004, *J.B.C.*, **279**, 27599-27606 (cited in the IDS on file) shows that CEL interacts with the scavenger receptor SR-BI.

- Rebaï *et al*, 2005 (but published electronically on 29 November 2004), *Arterioscler. Thromb. Vasc. Biol.*, **25**, 359-364 (cited in the IDS on file) shows that CEL (which it refers to as "BSDL") can interact with the extracellular matrix (ECM) on epithelial cells, thereby displacing the normally bounds growth factors bFGF and VEGF. This paper makes the point that this activity is due to structure, rather than enzymatic activity – please see page 363, 2nd column, lines 2-5.

- McKillop *et al*, January 2004, Acta Pædiatr., **93**, 10-16 (cited in the IDS on file) shows that the C-terminal part of CEL (which it refers to as "BSSL") contains Lewis x and b antigenic structures, which is said to suggest an adhesive function in cell-cell interactions (see final sentence of the abstract).

Thus, there is clear evidence that CEL can interact ***both*** with atherogenic lipoproteins in the plasma ***and*** with vascular endothelial receptors, which supports its role as a ***bridging molecule*** in the promotion of binding and retention of atherogenic lipoproteins to vascular endothelium in atherosclerosis.

This activity is also supported by Kodvawala *et al*, 2005, *J. Biol. Chem.*, 280, 38592-38598 (cited in the IDS on file) which shows that atherosclerosis is promoted by the expression of CEL in mouse macrophages (ordinarily mouse macrophages do not express CEL). Macrophages play a key role in the development of atherosclerotic plaques in the endothelium, as discussed in the present application at page 1, lines 28-29. This result clearly supports the pro-atherogenic role of CEL.

The new claims presented above define ***specific types*** of "receptors" for CEL (*i.e.*, molecules that strongly bind CEL) that are either present in the vascular endothelium, or represent plasma-derived atherogenic lipoprotein components, as summarized in Table A.

Table A: Categorization of CEL receptors listed in Claim 1

Vascular Endothelial Receptors	**Receptors associated with atherogenic lipoproteins in the plasma**
Vascular proteoglycans	Lipoprotein lipase
Scavenger receptors	Apolipoproteins
AGE receptors	Lipoproteins and lipoprotein particles

As will be readily apparent from the foregoing explanation, since the applicant has realised that CEL can act as a "bridging molecule" between factors in the blood vessel wall and atherogenic factors in the plasma, then compounds that disrupt CEL's binding to either, or both, of the above categories of factors (*i.e.*, receptors) should be useful in decreasing retention of atherogenic lipoproteins in atherogenesis and so their importance in decreasing or inhibiting atherogenesis will be evident.

IV. Rejections Under 35 U.S.C. §112

A. Second Paragraph

Claim 4 is rejected as indefinite. Applicants traverse, but in the interest of advancing the prosecution, claim 4 has been rendered dependent upon claim 1. More particularly, it is now specified in claim 4 that the test agent used must be a compound that has already been identified by the method of amended claim 1 as being able to decrease CEL binding to at least one of the specified receptors. Reconsideration and withdrawal of the rejection is therefore respectfully requested.

B. First Paragraph – Enablement

The examiner has objected to the "useful..." language in previous claims 1, 2 and 4. This rejection has been rendered moot by the amended set of claims in which such language is deleted.

The examiner also alleges that "the claims require that the modulation of binding of CEL to a receptor is an indication of whether a compound is ***useful for*** prevention and treatment of atherosclerosis or reducing the retention of atherogenic lipoproteins in atherogenesis" (emphasis added), and further alleges that the application fails to provide evidence as to whether CEL is a cause or symptom of atherosclerotic lesions. Applicants disagree, as it is clear that CEL can have a role in promoting atherogenesis by virtue of its ability to act as a "bridging molecule" between vascular endothelial receptors and plasma-borne atherogenic lipoprotein components, as discussed above.

Furthermore, there is strong evidence that CEL can promote atherosclerosis. This is evidenced by the expression of CEL in mouse macrophages (which do not normally express CEL) and this has been shown to ***promote*** atherosclerosis (see abstract of Kodvawala *et al,* 2005,

J. Biol. Chem., 280, 38592-38598) which supports a role for CEL in the development of atherosclerosis. Thus, even if the examiner's comments are believed to still apply to the amended claims, it is clear that the reduction of binding of CEL to either or both of its vascular or lipoprotein receptors is likely to affect the development of atherogenesis.

The examiner has referred to a "vast and varied genus" of suitable receptors as discussed in the specification and questions which would have a role in atherogenesis. However, this issue has been rendered moot by the fact that the claims have been amended to refer to specific types of receptors which are reasonably understood to play a role in the mechanism of endothelial retention of atherogenic lipoproteins which underlie the development of atherosclerotic lesions.

The examiner also alleges that the application fails to teach which form of modulation (increasing or decreasing) of binding of CEL to a receptor is required to reduce retention of atherogenic lipoproteins. Again, the claims have been amended to refer to compounds that are able to ***decrease*** the binding of CEL to a receptor, and thus this point too is rendered moot.

The examiner also alleges that Bengtsson-Ellmark *et al*, 2004, *Eur J Hum Genetics*, 12, 627-632, supports the view that the role of CEL in atherogenesis was not predictable at the time of filing. This appears to be with regard to the ***enzymatic*** role of CEL. However, CEL's ability to act as a "bridging molecule" in the context of the present invention is more likely to be reliant on its ***structural*** properties, which is different from its actions as an enzyme.

Again, applicants point to Gustafsson *et al.*, page 6, 2nd column, lines 15-16 which reports that, when LPL acts as a bridging molecule "The bridging function of LPL does not require catalytic activity." Likewise, Rebaï *et al.* makes the point that the ability of CEL to interact with the extracellular matrix (ECM) on epithelial cells is due to structure, rather than enzymatic activity (see page 363, 2nd column, lines 2-5). Thus, it is clear that the enzymatic

activity of CEL is not likely to be relevant in the context of its action as a "bridging molecule" in the recruitment and retention of atherogenic lipoproteins in the vascular endothelium during atherogenesis.

The examiner also alleges that previous claim 4 additionally lacks enablement because the specification allegedly fails to teach "one or more procedures to measure the ability of the test compound to reduce the retention of atherogenic lipoproteins." However, there is no requirement for the specification to teach such a procedure in order for the skilled person to practice it without undue difficulty, since methods of assessing the retention of atherogenic lipoproteins in the extracellular cell matrix (ECM) were well known in the art at the priority date of the application (2 April 2004). For example:

- Auerbach *et al*, 1999, *Atherothrombosis*, 142; 89-96 discloses an *in vitro* method for assessing the effect of lipoprotein lipase (LPL) on the binding (or retention) of [^{125}I]Lp(a) – a lipoprotein associated with atherosclerosis - to the ECM. Section 2.3, on pg 91, of the article sets out the protocol used for assessing retention of [^{125}I]Lp(a). Additionally, the effect of different molecules, such as heparin or polylysine, on the binding of [^{125}I]Lp(a) was also assessed, indicating that the effect of ***any*** molecule on the retention of [^{125}I]Lp(a) can also be determined.

  As disclosed in the present application, CEL also acts as a bridging molecule in a similar fashion to LPL, which has been shown in the prior art to act as a bridging molecule. By using this method, the person skilled in the art would be able to determine if a test compound could disrupt the retention of lipoproteins observed in the presence of CEL.

- Olin-Lewis *et al*, 2002, *Circ Res.*, 90; 1333-1339 also uses an *in vitro* assay for measuring the binding of HDL to the ECM (in this case, generated by cultured arterial smooth muscle cells). The matrix binding assay is detailed on page 1334 of the article, column 2, 2nd paragraph, where the ability of HDL_3+/-E to bind to vascular ECM was determined using a modified ELISA plate assay.

  Additionally, Olin-Lewis *et al* also describes an *in situ* method for evaluating the retention of HDL by the artery wall of perfused carotid arteries of mice by using fluorescently-labelled (DiI) HDL. This protocol is also detailed on page 1334.

- Skålén *et al*, 2002, *Nature*, 417; 750-754 discloses another *in situ* method for assessing the retention of ^{125}I-LDL, and proteoglycan-binding defective ^{125}I-LDL, in perfusion fixed aortas of mice (see page 751, column 1, 4th paragraph).

The skilled person, without undue burden, and using an entirely routine level of skill in the art, would be able to use any of the methods disclosed above, to test the ability of the test compound (which disrupts the interaction between CEL of its receptors) to reduce the retention of atherogenic lipoproteins both *in vitro* and *in situ*.

The examiner also alleges that it is not clear how such a procedure could be designed in the absence of a specific molecule that CEL binds to. As the receptors to which CEL binds have been identified in the claims, the person skilled in the art can appreciate which interactions must be disrupted in order to reduce the retention of atherogenic lipoproteins caused by CEL.

Therefore, the skilled person is readily able to select and adapt any of the known methods in the prior art to determine if a test compound is able to reduce the retention of atherogenic lipoproteins.

Reconsideration and withdrawal of the rejection is therefore respectfully requested.

C. First Paragraph – Written Description

As discussed above, the claims have been amended to define specific categories of receptors and, as explained, these are either receptors present on the vascular endothelium or are plasma-borne components of atherogenic lipoproteins; in its role as a "bridging molecule," CEL can bind to both types of receptors to bring about the subendothelial retention of atherogenic lipoproteins, which in turn promotes the development of atherogenesis.

As the receptors to which CEL binds have been identified in the claims and in the specification (specification on page 7, lines 3 to 14), and since they have a well-explained role in atherogenesis, it follows that the claims relate to subject matter that was described in the

specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Moreover, it is not necessary for the specification to outline specific methods by which the skilled person could determine whether a test compound has the ability to reduce the retention of atherogenic lipoproteins, as such methods were clearly available to the person skilled in the art at the priority date of the invention (2 April 2004), as already discussed. *Hybritech v. Monoclonal Antibodies*, 802 F.2d at 1384, 231 USPQ at 94; *Fonar Corp. v. General Electric Co.*, 107 F.3d at 1549, 41 USPQ2d at 1805 (The description need only describe in detail that which is new or not conventional).

Reconsideration and withdrawal of the rejection, in light of the amendments and comments above, is respectfully requested.

V. Rejection Under 35 U.S.C. §102

The examiner alleges that Lange *et al.* teaches a method of identifying a compound which comprises assaying the agent for its ability to modulate the binding affinity of pancreatic cholesterol esterase (PCE) to a receptor (PCE^R), PCE being another known name for CEL. Applicants traverse.

Lange *et al.* relates to methods and agents for inhibiting the binding of PCE to a specific ***intestinal*** receptor protein, designated PCE^R, in order to block uptake of dietary cholesterol. Lange *et al.*, col. 3, lines 7-28 describes the human PCE^R specifically as a glycoprotein that contains the glycosaminoglycan derivative heparin (lines 21-28), *i.e.*, it is a proteoglycan, isolated from the human ***colon*** carcinoma cell line CaCo-2 (lines 14-16 and 29-31). Thus, the receptor used in Lange *et al.* is an ***intestinal*** (colonic) proteoglycan, not a ***vascular*** proteoglycan as recited in amended claim 1. Nor is there any indication in the art that the receptor described in

Lange *et al.* can be considered to be any of the other types of receptors defined by new claim 1, that is, scavenger receptors, AGE receptors, lipoprotein lipase, apolipoproteins, lipoproteins or lipoprotein particles. Thus, amended claim 1 relates to a method that uses ***different receptors*** than the receptor disclosed in Lange *et al.*, and so is clearly novel.

Furthermore, the method of amended claim 1 is performed for a ***different purpose*** than that described in Lange *et al.*, which is alleged to be useful to identify agents capable of the treatment or prevention of atherosclerosis ***through inhibition of the dietary uptake of cholesterol*** in patients (a presumed risk factor for atherosclerosis). The enzymatic activity of CEL present in circulation has previously been suggested to affect the lipoprotein profile. However, the present inventors were the first to realize that CEL present in lipoprotein particles can act as a bridging molecule and that binding of CEL to a receptor as defined in amended claim 1 can contribute to the retention of atherogenic lipoproteins.

Reading Lange *et al.* without the new understanding provided in the present application, the person skilled in the art would only consider screening for agents capable of inhibiting the ***dietary uptake of cholesterol*** in patients, and would address this problem by using an ***intestinal*** proteoglycan CEL receptor of the type described in Lange *et al.* There is no reason, when screening for agents capable of inhibiting the ***dietary uptake of cholesterol*** in patients, for the person skilled in the art to consider using the alternative receptor types listed in amended claim 1 – they are all receptors active in ***vascular tissue or plasma in the vascular system*** and are not related to the uptake of dietary cholesterol. This provides yet another novel distinction as compared to Lange *et al.*

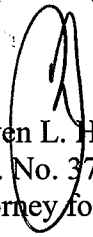
Moreover, there would be no reason for the person skilled in the art, considering Lange *et al.* to consider modifying its method such that it uses a ***vascular*** proteoglycan as the CEL

receptor instead of its ***intestinal*** proteoglycan receptor. It would make no sense to do so, because the skilled reader of Lange *et al.* is focussed on attempting to inhibit the dietary uptake of cholesterol and so would persist in using ***intestinal*** receptors of CEL. The skilled reader would similarly find no motivation in Lange *et al.* to derive the present invention.

VI. Conclusion

The Examiner is invited to contact the undersigned attorney with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,



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